REMARKS

Claims 38, 39, 44-51, 53, 60, 73-76, and 81-83 are pending in the application and have been examined. Claims 38, 39, 44-51, 53, 60, 73-76, and 81-83 stand rejected. Claim 60 has been withdrawn. Claims 38 and 73 have been amended. No new matter has been introduced. Reconsideration and allowance of Claims 38, 39, 44-51, 53, 73-76, and 81-83 is respectfully requested.

The Rejection of Claim 60 Under 35 U.S.C. §112

Claim 60 stands rejected under 35 U.S.C. §112 as being indefinite because it is dependent on a previously withdrawn claim. Claim 60 has been withdrawn. Removal of this ground of rejection is respectfully requested.

The Rejection of Claims 38, 39, 44-51, 73-76, and 81-83 Under 35 U.S.C. §103(a) as Being Unpatentable Over U.S. Patent No. 5,858,355 (Glorioso et al.)

Claims 38, 39, 44-51, 73-76, and 81-83 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,858,355 (Glorioso et al.).

The Examiner characterizes Glorioso et al. as disclosing a method of treating cartilage damage via direct injection to the knee of a patient in need (Col. 6, lines 35-50). As noted by the Examiner, the formulation disclosed in Glorioso et al. "comprises genetic material that encodes for a cytokine such as TGF beta 1 and 2 and at least an interleukin receptor antagonist (col. 18, line 65-col. 19, line 18)." (Emphasis added.) The Examiner further characterizes Glorioso et al. as disclosing that the compound can be used to either prevent or further treat arthritis via injections. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to treat a wide range of degenerative disorders including arthritis in view of the combined

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teachings of Glorioso et al. Applicants respectfully traverse this ground of rejection for the following reasons.

As an initial matter, while not acquiescing to the Examiner's position, but in order to clarify the invention, Claims 38 and 73 have been amended to recite, in relevant part:

> delivering to the joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective agent that directly promotes cartilage anabolic processes and the second chondroprotective agent is an inhibitor of cartilage catabolism, and the solution is delivered locally to the joint...wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes . . . .

Support for this amendment is found in the specification (published as WO 01/07067) at page 34, line 35, to page 35, line 3.

Glorioso et al. fails to render the claimed invention unpatentable. *KSR* confirmed that the Grahm Factor Analysis should be used in determining whether a claimed invention is obvious under Section 103(a). *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). This analysis includes assessing the rejected claims, the scope and content of the cited art, and the differences between the rejected claims and the cited art. *Id.* at 1734. As will be shown, a *prima facie* case of obviousness has not been established because (1) Glorioso et al. fails to teach every limitation

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of the claimed invention, and (2) there is no motivation or expectation of success to modify Glorioso et al. as proposed by the Examiner to arrive at the claimed invention because Glorioso et al. teaches directly away from the claimed invention.

1. The Differences between the Rejected Claims, as amended, and the Cited Art

Glorioso et al. is generally directed to methods of introducing at least one gene encoding a product into at least one cell of a connective tissue of a mammalian host for use in treating the mammalian host (i.e., gene therapy). See e.g., abstract. As stated in Glorioso et al., "The present invention discloses ex vivo and in vivo techniques for delivery of a DNA sequence of interest to the connective tissue cells of the mammalian host." Col. 1, lines 31-33. "The in vivo technique bypasses the requirement for in vitro culture of target connective tissues; instead relying on direct transplantation of the DNA sequence, DNA vector or other delivery vehicle to the target in vivo connective tissue cells, thus effecting expression of the gene product of interest." Col. 1, lines 41-46 (emphasis added). Glorioso et al. further states:

> It has been shown that genetic material can be introduced into mammalian cells by chemical or biologic means. Moreover, the introduced genetic material can be expressed so that high levels of a specific protein can be synthesized by the host cell. Cells retaining the introduced genetic material may include an antibiotic resistance gene thus providing a selectable marker for preferential growth of the transduced cell in the presence of the corresponding antibiotic. [Col. 3, lines 32-39.]

As further stated in Glorioso et al., "This method includes employing genes having DNA that is capable of maintenance and expression." Col. 37, lines 24-26. In one embodiment, Glorioso et al. discloses the use of a viral vector comprising at least one gene capable of

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encoding a list of various agents, including a cytokine such as TGF beta 1 and 2 and at least an interleukin receptor antagonist (Col. 18, line 65, to Col. 19, line 18).

In sharp contrast to the gene therapy methods of Glorioso et al., the methods of the present invention are directed to delivering to a joint a composition in solution comprising a therapeutically effective amount of a first chondroprotective agent and a therapeutically effective amount of a second chondroprotective agent, wherein the first chondroprotective agent is an anabolic chondroprotective agent that directly promotes cartilage anabolic processes, wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes.

As described in the instant specification, exemplary anabolic chondroprotective agents that directly promote cartilage anabolic processes are selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes, including proteins or peptides.

For example, as stated in the specification, "Transforming growth factor-beta (TGF-beta) subfamily members are 25 kD pleiotropic, multifunctional proteins . . . ." Page 47, lines 25-26. As further stated in the specification, "Bone morphogenetic proteins (BMPs) are multifunctional regulators of cell growth, differentiation and apoptosis that belong to the transforming growth factor (TGF-beta) superfamily." Page 48, lines 12-14.

As further stated in the specification:

> Naturally occurring TGF-beta and BMP agonists as well as synthetic or human recombinant (rh) agonists suitable for use in the cartilage-

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protective solution of the present invention may interact with any of the BMP receptors described above. As used herein, the term 'TGF-beta and BMP agonists' includes fragments, deletions, additions, amino acid substitutions, mutations and modifications thereof which retain the biological characteristics of the naturally occurring human TGF-beta and BMP agonist ligands. [Specification at page 49, lines 4-10.]

As further described in the specification,:

> Within the context of defining TGF-beta and BMP agonists as pharmacological agonists, the term TGF-beta and BMP agonists includes, but is not limited to: (1) peptide sequences which correspond to naturally (endogenous) produced amino acid sequences or fragments thereof, (2) recombinant TGF-betas and BMPs which are truncated or partial sequences of the full length naturally occurring TGF-beta and BMP amino acids which retain the ability to bind cognate their respective receptor and retain biological activity and analogs thereof, and (3) chimeric TGF-betas and BMPs which are recombinant polypeptides comprised of truncated or partial sequences corresponding to a portion of the full length amino acid sequences attached through oligomers (e.g., amino acids) to a sequence corresponding to a portion of an IgG polypeptide (e.g., IgG hinge and Fc domain) which retain the ability to bind the cognate receptor and retain biological activity. [Specification at page 51, lines 10-21.]

As described in the specification, the local delivery of the drug combination of the present invention achieves "an instantaneous therapeutic concentration of chondroprotective agents within the joint." Page 36, lines 7-9. As further stated in the specification, an advantage

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of the present invention is that "direct, local delivery to the joint enables use of novel, pharmaceutically active peptides and proteins, including cytokines and growth factors, which may not be therapeutically useful if limited to systemic routes of administration." Specification at page 36, lines 14-17.

Therefore, it is demonstrated that Glorioso et al. does not teach or suggest a method of inhibiting cartilage degradation comprising delivering to the joint a composition comprising an anabolic chondroprotective agent that directly promotes cartilage anabolic process in combination with an inhibitor of cartilage catabolism, as claimed.

2. The Differences between the Rejected Claims and the Cited Art Are Not Obvious Differences

There is no apparent reason to modify the methods of Glorioso et al. as proposed by the Examiner to replace the genetic material encoding various proteins with an anabolic chondroprotective agent that directly promotes cartilage anabolic processes (e.g., proteins or peptides), wherein the anabolic chondroprotective agent is selected from the group consisting of members of the transforming growth factor-β superfamily, including TGF-β agonists and bone morphogenic protein agonists, that promote cartilage anabolic processes, and insulin-like growth factors that promote cartilage anabolic processes, in order to arrive at the claimed invention. As stated in M.P.E.P. § 2143.01, "Rejections on obviousness cannot be sustained by mere conclusory statements, instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusions of obviousness." M.P.E.P. § 2143.01, citing *KSR*, 127 S.Ct at 1741, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). In the context of an obviousness rejection, the Supreme Court explained the importance of "identify[ing] a reason" why a skilled artisan would be prompted to arrive at the presently claimed invention. *KSR*, 127 S.Ct. at 1741.

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As noted above, Glorioso et al. discloses a gene therapy approach that relies on transplantation of a DNA sequence into the target *in vivo* connective tissue cells, thus effecting expression of the gene product of interest. As described in Glorioso et al., "The introduced genetic material can be expressed so that high levels of a specific protein can be synthesized by the host cell. Cells retaining the introduced genetic material may include an antibiotic resistance gene thus providing a selectable marker for preferential growth of the transduced cell in the presence of the corresponding antibiotic." Col. 3, lines 32-39.

Moreover, Glorioso et al. actually teaches directly away from the claimed invention by describing the disadvantages of an approach involving intra-articular administration of agents that directly promote cartilage anabolic processes, such as proteins or peptides. Glorioso et al. states,"[I]ntra-articular injection of joints provides direct access to a joint. However, most of the injected drugs have a short intra-articular half life. The present invention solves these problems by introducing into the connective tissue of a mammalian host genes encoding for proteins that may be used to treat the mammalian host." Col. 15, lines 14-20. Glorioso et al. further states:

> Thus, the access of large drug molecules, for example, proteins, to the joint space is substantially restricted. Intra-articular injection of drugs circumvents those limitations; however, the half-life of drugs administered intra-articularly is generally short. Another disadvantage of intra-articular injection of drugs is that frequent repeated injections are necessary to obtain acceptable drug levels at the joint spaces for treating a chronic condition such as, for example, arthritis. [Col 3, lines 15-23.]

Therefore, it is demonstrated that Glorioso et al. does not teach or suggest the present invention. Moreover, Glorioso provides no motivation or expectation of success to arrive at the claimed invention because it teaches directly away from the present invention. A reference may

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be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that was taken by the applicant. *Tec Air Inc. v. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999)). That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness. See *Winner Int'l Royalty Corp. v. Wang*. 202 F.3d 1340, 1349-50 (Fed. Cir. 2000)).

3. Evidence of Unexpected Results Demonstrates the Patentability of the Rejected Claims

As stated in M.P.E.P. § 2142, "If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." However, despite the absence of a *prima facie* case of obviousness, in order to facilitate prosecution, applicants previously submitted an extensive collection of data during prosecution of the present application, summarized in applicants' last response, dated March 23, 2009, demonstrating the unexpected results of the present invention including (1) non-prior art references (publications by Studer et al.) that were submitted with the response filed by applicants on January 3, 2006; and (2) additional experimental data that was submitted with the response filed by applicants on November 6, 2006. The experimental data previously provided by applicants is commensurate in scope with the pending claims, as amended, and demonstrates the surprising and remarkable effect that the evaluated inhibitors of cartilage catabolism, when administered together with an anabolic chondroprotective agent that directly promotes cartilage anabolic processes, have the potential to not only inhibit inflammation and matrix degradation, but to also restore the ability of the diseased chondrocytes to respond to the evaluated anabolic growth factors.

Thus, without the benefit of the applicants' disclosure, one of skill in the art would not be motivated by the teachings of the cited references, or by general knowledge in the art, to arrive at the claimed invention, and would have no reasonable expectation of success in practicing the

invention as claimed. Accordingly, because the cited references teach directly away from the claimed invention, and because the general knowledge of one skilled in the art would not provide any basis or motivation to arrive at the claimed invention, Claims 38, 39, 44-51, 53, 73-76, and 81 are believed to be clearly patentable under 35 U.S.C. § 103(a) over U.S. Patent No. 5,858,355 (Glorioso et al.). Removal of this ground of rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, applicants respectfully submit that all of the pending claims are in condition for allowance. Reconsideration and favorable action is requested. The Examiner is further requested to contact the applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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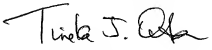

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